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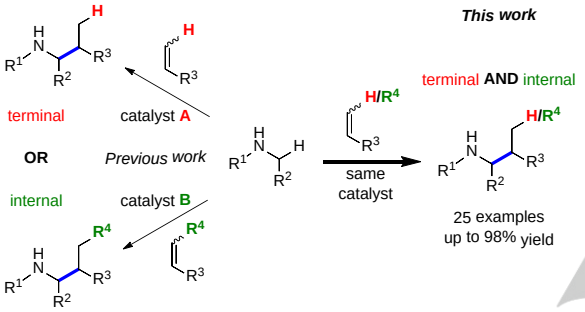
Planar-chiral [2.2]Paracyclophane-based Pyridonates as Ligands for Tantalum-catalyzed Hydroaminoalkylation

Carolin Braun [a,b],, Martin Nieger [c], Stefan Bräse *[a,d], and Laurel L. Schafer *[b]

Abstract: By using planar chiral [2.2]paracyclophane-containing *N,O*-chelating ligands for tantalum-catalyzed hydroaminoalkylation, one of the most versatile catalytic systems for this reaction to date was obtained. Convenient C_{sp3}–C_{sp3} bond formation of amines with terminal and internal alkenes was enabled by the same *in situ* synthesized catalytic system of [2.2]paracyclophane-based pyridonates and $Ta(CH_2TMS)_3Cl_2$ (Scheme 1) that shows also very promising results for *N*-containing heterocycles.



Scheme 1. Intermolecular hydroaminoalkylation.

Amines as nitrogen containing compounds are important target structures for fine chemicals, agrochemicals and pharmaceuticals. In the past, numerous methods have been explored to construct substituted amines of defined stereochemistry. The majority of these approaches focus on either C–N bond formation as the crucial step, such as palladium catalyzed Buchwald-Hartwig[1] coupling, or on C–C bond formation by the addition of nucleophiles to imines[2] or enamines[3]. These methods typically require pre-activated or functionalized substrates and therefore more sustainable approaches using common feedstock chemicals to access functionalized amines are an area of focus. This can be achieved by the catalytic hydrofunctionalization of alkenes, such as hydroamination[4] and hydroaminoalkylation[5]. Recent advances in hydroamination have exploited photoredox catalysis to overcome the inherent thermodynamic challenge of alkene hydroamination.[6]

Hydroaminoalkylation is an atom economic tool that formally inserts an alkene into a C-H bond of an alkylamine. The main advantages of hydroaminoalkylation are that it is 100% atom economic and it avoids the use of stoichiometric additives or the installation of directing/protecting groups. By using low-toxicity early transition metals like Ti[7], Ta[8], or various others[9], significant advances have been realized, resulting in several catalysts for the transformations of aniline derivatives with terminal or internal[8q] alkenes (Scheme 1). Nevertheless, there is a lack of versatile catalyst systems. To date there is no hydroaminoalkylation catalyst capable of mediating reactivity with both internal and terminal alkenes or with a broad range of alkyl and aryl amines. $TaMe_3Cl_2$ has been reported to catalyze the hydroaminoalkylation with terminal and internal alkenes, but with only moderate yields for terminal alkenes and without being useful for *N*-heterocycles.[8l] Moreover, there are only a few reported systems for asymmetric hydroaminoalkylation,[8e-i] which is a key objective for assembling many target compounds of importance to the pharmaceutical industry. We could address these limitations by identifying a catalyst system that can realize the hydroaminoalkylation of terminal and internal alkenes by incorporating a planar chiral [2.2]paracyclophane backbone into pyridone and amide proligands (Figure 1). Notably, such *N,O*-chelating proligands have shown very promising hydroaminoalkylation reactivity to date,[5a, 8e, 8m, 8o, 8q] and modification of proligand steric bulk has been shown to be key for realizing improved substrate scope.[8o] The [2.2]paracyclophane moiety contributes two important attributes to these proligands; its rigid and bulky structure should increase the generality of the hydroaminoalkylation reaction, as steric bulk improves activity. Its planar chirality presents the opportunity to conduct asymmetric catalysis.

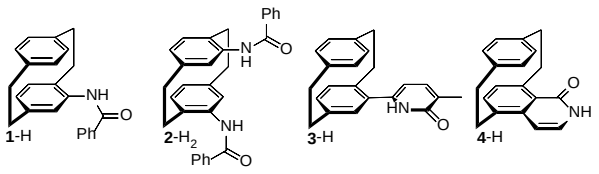


Figure 1. Selected [2.2]paracyclophane containing amides (**1**, **2**) and pyridones (**3**, **4**) as *N,O*-chelating proligands.

First, we exploited known synthetic sequences to prepare *N,O*-chelating ligands based on the [2.2]paracyclophane backbone.

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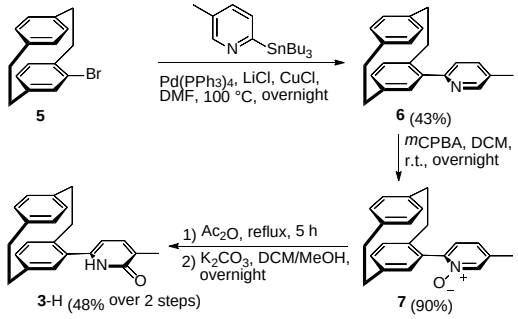
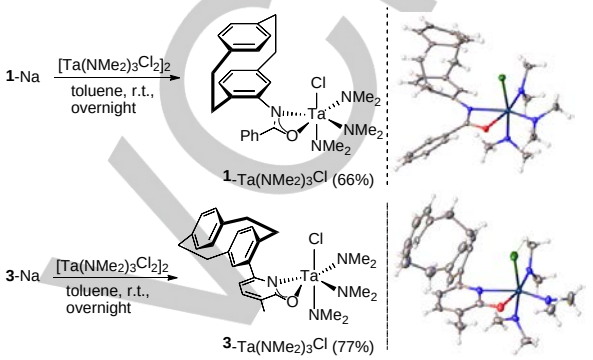
Mono(amide) **1**-H as well as tethered bis(amide) **2**-H_2 were synthesized as previously reported from the corresponding racemic and enantiopure amines by condensation reactions with benzoyl chloride.[10] Pyridonate complexes of Ta have shown particularly impressive reactivity manifolds in hydroaminoalkylation.[8m, 8p] Thus, two [2.2]paracyclophanes of different rigidity **3**-H and **4**-H have been selected. The synthetic route of the pyridone-substituted [2.2]paracyclophane **3**-H is based on the pyridine intermediate **6** that can be obtained by Stille cross-coupling of **5** using $Pd(PPh_3)_4$ with CuCl and LiCl as additives.[11] The pyridine **6** can be transformed into the pyridone **3**-H using the standard procedure by oxidation with *m*CPBA to the respective pyridine-*N*-oxide **7** followed by a rearrangement reaction[12] in refluxing acetic anhydride to give, after hydrolysis of the *N*-acetylated pyridone, the desired proligand **3**-H (Scheme 2).



Scheme 2. Synthesis of pyridine-substituted [2.2]paracyclophane **3**-H.

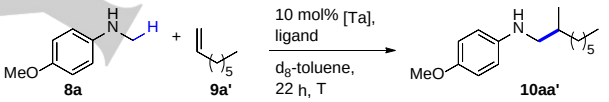
The synthesis of **4**-H starting from **5** has been described by Ruzziconi *et al.*[13] in their isochinolinophane synthesis. In this work the condensation reaction of 4-carboxy[2.2]paracyclophane with aminoacetaldehyde dimethyl acetal followed by the ring closing reaction in polyphosphoric acid gives **4**-H in a good overall yield (57%).[13-14] Notably, all of these ligands can be obtained in their enantiopure form by separation of the enantiomers of the racemic bromide intermediates by preparative HPLC on chiral stationary phase (Chiralcel® AZ-H column). Subsequent reactions as described for the racemic ligands results in the preparation of enantiopure materials. Alternatively, there is a less favored approach that does not require preparative HPLC using the chiral resolution of 4-formyl[2.2]paracyclophane *via* diastereomeric imines that can be separated by fractional recrystallization.[10] After hydrolysis of the imines, the aldehyde has to be transformed into the appropriate intermediates by Kröhnke pyridine synthesis to build up the pyridine **6** or oxidation to the carboxylic acid as the starting material for **4**.[14]

The targeted amidate or pyridonate tantalum complexes were synthesized by salt metathesis in good yields (Scheme 3). Previously reported $TaMe_3Cl_2$[8l] and phosphoramidate-$TaMe_3Cl$[8j] complexes are sensitive towards temperature and light, therefore dimethylamido ligands have been selected for improved robustness.[8k, 8m, 8p] The solid state molecular structure of both, the amidate complex **1**-$Ta(NMe_2)_3Cl$ and the pyridonate complex **3**-$Ta(NMe_2)_3Cl$, reveal a distorted octahedral geometry. Furthermore, there is asymmetric binding of the κ^2-*N,O*-chelate of the ligands on tantalum [**1**-$Ta(NMe_2)_3Cl$: Ta–N 2.229 Å, Ta–O 2.219 Å; **3**-$Ta(NMe_2)_3Cl$: Ta–N 2.289 Å, Ta–O 2.175 Å] that illustrates the differences between amidate and pyridonate ligands as well as the impact of the bulky paracyclophane on the coordination environment about the metal center. The axial chloro ligand and Ta–NMe_2 bond lengths that are comparable to those reported in literature for pyridonate[8m] or amidate[8e, 8o] tantalum complexes. A comparison of the metric parameters of the protioligand **3**-H (see supporting information) with **3**-$Ta(NMe_2)_3Cl$ shows elongation of the C=O double bond as well as a reduction of the OCN angle upon metal complexation.



Scheme 3. Synthesis of [2.2]Paracyclophane-containing Tantalum Complexes.

Table 1.[15] Selected results of the *in situ* screening for 1-octene as terminal alkene.[a]



Entry	Ligand	Tantalum Precursor	Temp.	Conversion
1	**1**-Na	$[Ta(NMe_2)_3Cl_2]_2$	90 °C	24% (33%)[b]
2	**1**-Na	$TaMe_3Cl_2$	90 °C	75%
3	**1**-Na	$Ta(CH_2TMS)_3Cl_2$	90 °C	55%
4	**2**-H_2	$Ta(NMe_2)_5$	160 °C	10%
5	**3**-Na	$TaMe_3Cl_2$	90 °C	>95%
6	**3**-Na	$[Ta(NMe_2)_3Cl_2]_2$	90 °C	>95% (>95%)[b]
7	**3**-Na	$Ta(CH_2TMS)_3Cl_2$	90 °C	>95%
8	**3**-H	$Ta(NMe_2)_5$	110 °C	65%
9	**4**-Na	$TaMe_3Cl_2$	90 °C	37%
10	**4**-Na	$[Ta(NMe_2)_3Cl_2]_2$	110 °C	>95% (>95%)[b]
11	**4-Na**	**$Ta(CH_2TMS)_3Cl_2$**	**110 °C**	**>95%**

[a] Reaction conditions: amine (0.50 mmol), 1-octene (0.75 mmol), tantalum precursor (0.05 mmol), proligand (0.05 mmol), d_8-toluene (0.5 mL). Conversion was determined by ^{1}H NMR spectroscopy. [b] Isolated complex.

In an effort to identify a catalyst system that can realize the. hydroaminoalkylation of both, terminal and internal alkenes, we performed an *in situ* protocol for catalyst screening using our ligands **1–4** with various tantalum precursors. First we

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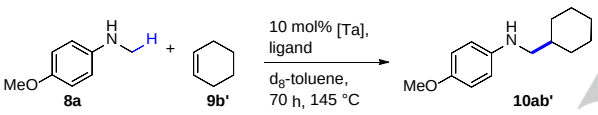
investigated the reactivity with the commonly used terminal alkene 1-octene (Table 1)[15]. The reactions were conducted at 90 °C initially and if no or only minimal reactivity was observed within 22 h, then the temperature of the reaction was raised as indicated. The *in situ* catalyst preparation results were compared with these of the isolated [2.2]paracyclophane-Ta(NMe_2)$_3$Cl complexes and were found to be comparable (entries 1, 6 & 10). The results show that hydroaminoalkylation with the complexes of amidate ligands **1** and **2** (entries 1–4) are inferior to the pyridonate ligands **3** and **4** (entries 5–11). The tethered bis(amidate) ligand **2** inhibited the reaction (entry 4) as the tantalum precursors will achieve full conversion for this benchmark reaction within 22 h at 145 °C. This result is reasonable with respect to the steric bulk of the tethered ligand that is shielding the Ta center. The catalyst activity depends not only on the *N,O*-chelating ligand, but also on the metal precursor as variable reactivity has been observed for ligands **1** (entries 1–3) and **4** (entries 9–11). In contrast, ligand **3** shows consistently high performance (entries 5–7) with different metal precursors, although an electron withdrawing chloro ligand seems to be crucial (entry 8). With ligands **3** the reaction can be performed at 70 °C with full conversion after 46 h.[15] The more rigid ligand **4** requires 110 °C for an effective quantitative conversion within 22 h (entries 10 & 11).

Table 2. *In situ* screening for cyclohexene as internal alkene.[a]

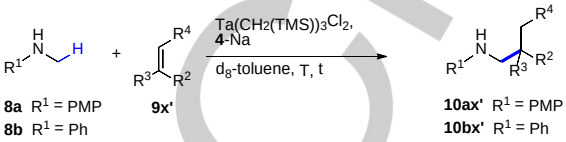


Entry	Ligand	Tantalum Precursor	Conversion
1	**1**-Na	[Ta(NMe_2)$_3$Cl$_2$]$_2$	n.r.
2	**1**-Na	Ta(CH_2TMS)$_3$Cl$_2$	n.r.
3	**3**-Na	$TaMe_3Cl_2$	63%
4	**3**-Na	[Ta(NMe_2)$_3$Cl$_2$]$_2$	54%
5	**3**-Na	Ta(CH_2TMS)$_3$Cl$_2$	24%
6	**4**-Na	$TaMe_3Cl_2$	48%
7	**4**-Na	[Ta(NMe_2)$_3$Cl$_2$]$_2$	12%
8	**4**-Na	Ta(CH_2TMS)$_3$Cl$_2$	>95%[b]

[a] Reaction conditions: amine (0.50 mmol), cyclohexene (0.75 mmol), tantalum precursor (0.05 mmol), proligand (0.05 mmol), d_8-toluene (0.5 mL). Conversion was determined by ^{1}H NMR spectroscopy. n.r. = no reaction. [b] 46 h reaction time.

Of particular interest was the reactivity with the known challenging internal alkene, cyclohexene. To date our group has reported a Ta pyridonate complex and a Ta ureate system as the examples of efficient catalysis of this reaction.[8m, 8p] Our *in situ* screening (Table 2) demonstrates this challenging transformation, requiring 145 °C and a prolonged reaction time of 70 h for reasonable conversions (>50%). Amidate ligand **1** is clearly inferior (entries 1–2), and bisamidate **2** was not tested due its poor activity for 1-octene. The dependence on the metal precursor is nicely illustrated by our results for the pyridonates **3** (entries 3–5) and **4** (entries 6–8). In both cases, the $TaMe_3Cl_2$ precursor (entries 3 and 6) shows better results than [Ta(NMe_2)$_3$Cl$_2$]$_2$ (entries 4 and 7) but is less attractive due to its propensity to decompose. Here the Ta(CH_2TMS)$_3$Cl$_2$ precursor has proven to be a more robust precursor[8q] while retaining excellent hydroaminoalkylation catalysis (full conversion after 46 h) when combined with pyridonate **4** (entry 8).

Table 3. Alkene Substrate Scope.[a]



8a R^1 = PMP
8b R^1 = Ph
9x'
10ax' R^1 = PMP
10bx' R^1 = Ph

Entry	Alkene	Product	Cond.	Yield (%)
1	**9a'**	**10aa'** **10ba'**	110 °C 22 h	90 68
2	**9b'**	10ab' 10bb'	145 °C 46 h	94 88
3	**9c'**	**10bc'**	145 °C 70 h	92
4	**9d'**	**10bd'**	145 °C 70 h	93 [4.0:1][b, c]
5	**9e'**	**10ae'**	145 °C 70 h	21
6	**9f'**	**10ae'**	145 °C 70 h	59
7	**9g'**	**10bg'**	145 °C 70 h	29
8	**9h'**	**10bh'**	145 °C 70 h	81 [1.1:1][b]
9	**9i'**	**10bi'**	145 °C 70 h	62 [4.7:1][b]
10	**9j'**	**10bj'**	145 °C 70 h	95
11	**9k'**	**10bj'**	110 °C 22 h	56
12	**9l'**	**10bl'**	110 °C 22 h	87
13	**9m'**	**10bm'**	110 °C 22 h	98
14	**9n'**	**10an'** **10bn'**	110 °C 22 h	97 94
15	**9o'**	**10bo'**	110 °C 22 h	25[c]
16	**9p'**	**10bp'**	110 °C 22 h	57

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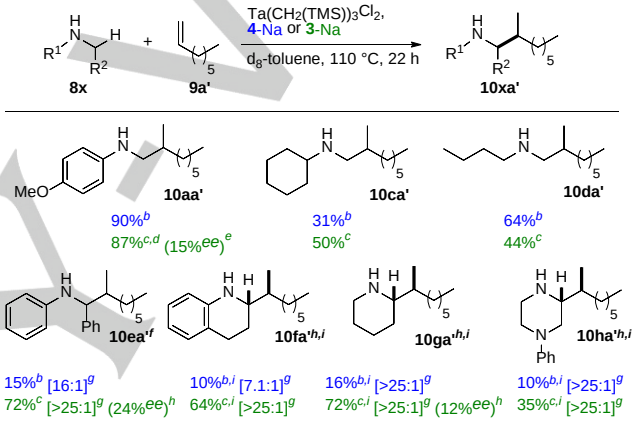
[a] Reaction conditions: amine (0.50 mmol), alkene (0.75 mmol), **4**-Na (0.05 mmol), $Ta(CH_2TMS)_3Cl_2$ (0.05 mmol), d_8-toluene (0.5 mL). cond. = reaction conditions. Isolated yield. [b] Major isomer presented. Yields refer to combined regioisomers. Ratio of regioisomers determined by GC of the inseparable purified products. [c] The *exo* configuration was determined by comparison with literature data.

Encouraged by the excellent hydroaminoalkylation reactivity for 1-octene and cyclohexene of the *in situ* prepared catalyst with the sodium salt of pyridonate **4** and $Ta(CH_2TMS)_3Cl_2$, we investigated its reactivity for a variety of internal and terminal alkenes (Table 3) and were impressed by a versatility that has not yet been reported for a single catalyst system. All products were isolated as the free amine demonstrating the viability of this approach for realizing atom efficient transformations. In general higher temperatures and longer reaction times were required for the internal alkenes. Linear internal alkenes (entries 5–7) are less reactive then cyclic alkenes (entries 2–4) with *Z*-alkenes (entries 6 and 7) being more reactive than *E*-alkenes (entry 5). For unsymmetrical alkenes the selectivity strongly depends on the explicit substrate with a varying degree of preference for addition of the methyl substituted carbon of the double bond resulting in a β-methyl branch on the resultant amine (entries 8–10). This preference reaches from almost statistic (entry 8) to highly selective in case of **9j'** (entry 10). Terminal alkenes allow for milder reaction conditions and exquisite regioselectivity for the branched product regardless of steric bulk (entries 1, 11-13) in moderate to excellent yields. Pleasingly, 1,1-disubstituted alkenes were transformed smoothly under the same reaction conditions to set the β-quaternary center in excellent yield (**9n'**, entry 14). More sterically demanding naturally occurring terpenes, such as β-pinene and limonene (entries 15 and 16) can undergo hydroaminoalkylation to yield selectively substituted chiral secondary amine products in one catalytic transformation. β-pinene results in the formation of only 1 diastereomer in modest yield while the hydroaminoalkylation of limonene at 110 °C proceeds with good selectivity for the terminal alkene and leaves the internal alkene unaffected.

With this unique alkene substrate scope in hand, we were interested to explore the amine substrate scope of our catalyst system (**4**-Na and $Ta(CH_2(TMS))_3Cl_2$, Scheme 4). Not only are *N*-methylanilines tolerated as amine substrates, but alkyl amines that include cyclohexyl (**10ca'**) or linear butyl (**10da'**) substituents can be used. Of particular interest were the more challenging amine substrates such as *N*-benzylaniline (**10ea'**) or *N*-containing heterocycles such as 1,2,3,4-tetrahydroquinoline (**10fa'**) piperidine (**10ga'**) or 1-phenylpiperazine (**10ha'**) that have been rarely reported.[8c, 8k] Despite the increased reaction temperatures required for reactions with heterocyclic amines (160 °C), we could obtain these products with high to excellent diastereoselectivities, albeit in low yield. Due to the excellent reactivity of ligand **3** with different tantalum precursors with 1-octene (Table 1), we performed the same reactions with **3**-Na and $Ta(CH_2(TMS))_3Cl_2$ using these more challenging amine substrates. The catalyst generated using **3**-Na and $Ta(CH_2(TMS))_3Cl_2$ resulted in drastically increased isolated yields while retaining excellent regioselectivities for these potentially pharmaceutical relevant amines **10ea'–ha'**. Furthermore, we performed the synthesis of **10aa'**, **10ea'** and **10ga'** with the enantiopure ligands *(RP)*-**3**-Na and *(SP)*-**4**-Na, respectively. Unfortunately, we observed only racemic products for the rigid *(SP)*-**4**-Na with the steric bulk pointing away from the metal center. However, *(RP)*-**3**-Na shows some asymmetric induction during hydroaminoalkylation catalysis resulting in *ee*'s of 12–24%*ee*. Although these *ee*'s are not yet synthetically relevant, this is the first example of enantioenriched[8e-i] *N*-heterocycles using hydroaminoalkylation and a promising starting point for further improvement of asymmetric hydroaminoalkylation. These results demonstrate that non-axial chiral ligands can be used for asymmetric hydroaminoalkylation and show that proximal placement of the chiral substituents to the metal center is critical for promoting good reactivity and selectivity, especially with desirable and challenging *N*-heterocycles.

Scheme 4. Scope of Amines.[a]



[a] Reaction conditions: amine (0.50 mmol), alkene (0.75 mmol), **4**-Na or **3**-Na (0.05 mmol), $Ta(CH_2TMS)_3Cl_2$ (0.05 mmol), d_8-toluene (0.5 mL). Isolated yield. [b] **4**-Na as proligand used. [c] **3**-Na as proligand used. [d] 90 °C. [e] Determined by chiral SFC of the tosylated amine. [f] Stereochemistry could not be determined. [g] Major isomer presented. Yields refer to combined regioisomers. Ratio of regioisomers determined by GC of the inseparable purified products. [h] Stereochemistry was determined by comparison with literature data. [i] 160 °C, 46 h.

In summary, we have developed the first [2.2]paracyclophane containing *N,O*-chelating ligands for the tantalum catalyzed hydroaminoalkylation of unactivated, sterically demanding terminal and internal alkenes. This *in situ* prepared precatalyst system enables the straight forward, atom-economic synthesis of β-substituted unprotected amines while avoiding co-catalysts, stoichiometric additives or the installation of directing groups. This reaction illustrates a sustainable approach for the rapid assembly of such selectively substituted amine products. We have demonstrated that a non-tethered [2.2]paracyclophane based ligand design can offer asymmetric induction as well as high reactivity, and can even tackle the hydroaminoalkylation of challenging *N*-heterocycles. Most importantly these investigations show how the catalytic system is influenced by the rigidity and bulkiness of the ligand system and the tantalum precursors. On-going work focuses on catalyst development toward chiral ligands that provide an appropriate balance between rigidity and steric bulk for improved reactivity and selectivity in asymmetric hydroaminoalkylation.

Experimental Section

Experimental details can be found in the Supporting Information which includes experimental procedures, compound characterization (^{1}H and ^{13}C spectra, PDF) and crystallographic data. (CIF: CCDC-1518241 (3H), CCDC-1518242 (4H), CCDC-1446990 (6) and CCDC-1518243 (7)). CCDC-1518241 (3H), CCDC-1518242 (4H), CCDC-1446990 (6) and CCDC-1518243 (7) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

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Keywords: Alkenes • Amines • Tantalum • Cyclophanes • Green chemistry

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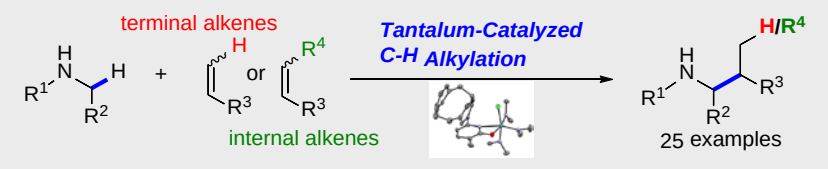

A synthetic route to [2.2]paracyclophane-containing *N,O*-chelating ligands and their first tantalum complexes was developed for use as hydroaminoalkylation catalysts. The *in situ* synthesized catalytic system enables the versatile C_{sp3}–C_{sp3} bond formation between terminal or internal alkenes and nitrogen containing heterocycles.

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Planar-chiral [2.2]Paracyclophane-based Pyridones as Ligands for Tantalum-catalyzed Hydroaminoalkylation